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Factors associated with multidrug-resistant *Pseudomonas aeruginosa* infection: a hospital-based case-control study

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KEYWORDS
Multidrug resistance; *Pseudomonas aeruginosa;* Mechanical ventilator; Endotracheal tube.

ABSTRACT
This study aimed to investigate the factors associated with multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) infection. The study was a hospital-based case-control study. Data were collected from medical records of patients with MDR-PA infection (110 cases) and without MDR-PA infection (110 controls) at the Roi Et Hospital between January 1, 2015 and December 31, 2017. Data analysis used statistics, univariable analysis, and multiple logistic regressions. Statistical significance was set at p-value < 0.05. Most of the 110 cases with MDR-PA infection were male (51.82 %) and the mean age was 61.82 ± 15.67 years, while most of the 110 controls were male (56.36 %) and the mean age was 55.01 ± 16.09 years. The multivariable analysis revealed that patients aged over 60 years (OR_{Adj} = 2.06, 95%CI = 1.14-3.71), admitted for more than 7 days (OR_{Adj} = 2.43, 95%CI = 1.28-4.60), underwent procedures involving an endotracheal tube (OR_{Adj} = 2.61, 95%CI= 1.42-4.80) and a mechanical ventilator (OR_{Adj} = 3.14, 95%CI= 1.67-5.88). Therefore, the risk factors for MDR-PA infection were patients who were admitted for more than 7 days, who underwent procedures involving an endotracheal tube and a mechanical ventilator.

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Introduction

The nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) is a major problem worldwide. These infection pathogens can cause serious problems because they are difficult to control. High mortality has been reported in patients with MDR-PA infection, especially those with septicemia[1,2]. The cost of treatment for MDR-PA is high. A study in Spain showed that the total economic cost per admission of a patient with MDR-PA was higher than that for non- multidrug resistant strains (EUR 15,265 and EUR 4,933, respectively)[3]. The risk factors for MDR-PA infection in China were patients who underwent tracheal intubation insertion, where a carbapenem was used, and hospitalization[4]. A study in Spain showed that bronchiectasis and the number of antibiotics used were independent factors for MDR-PA infection[5]. A study in Italy reported that the risk of MDR-PA septicemia was highest in patients who had a central venous catheter, previous antibiotic therapy, and corticosteroid therapy[6]. The prevalence of nosocomial infection in Thailand was reported to be highest with *Pseudomonas aeruginosa* followed by *Klebsiella* spp., *Acinetobacter baumannii*, Methicillin-resistant *Staphylococcus aureus*, and *Enterococci* spp., respectively[7]. However, despite the high prevalence and increasing numbers of MDR-PA, reporting on the risk of MDR-PA infection among Thai populations is rare. The aim of this study was to investigate the factors associated with MDR-PA infection.

Materials and methods

A hospital-based case-control study (control: case = 1:1) was used. All variables of interest were retrieved from medical records from the period January 1, 2015 to December 31, 2017. In total, there were 110 cases of patients diagnosed with MDR-PA infection and 110 controls were selected without MDR-PA infection.

Ethics consideration

This research was approved by the Ethics Committee for Human Research at Roi Et Hospital, Thailand (reference number 034/2560).

Criteria of cases

All of the 110 cases were the first diagnosis of *MDR-PA* infection, were admitted for more than 48 hours and were older than 15 years with no previous reported bacterial infection. All cases were confirmed diagnosis by physicians following the standard guidelines from the Department of Infectious Controls based on culture and sensitivity testing results for each of the study subjects.

Criteria of controls

None of the 110 controls had MDR-PA infection, none of them had reported for others bacterial infection and were randomly selected from patients who had been admitted on the same day as the cases, having been admitted for more than 48 hours and were older than 15 years.

Variables of interests

The variables of interest were: 1) general characteristics: sex, age, education, marital status, occupational, complication, duration of admission, and ward admitted to; and 2) risk factors from exposure to medical procedures: mechanical ventilator, urinary catheterization, endotracheal tube, and surgery. All variables were categorized into two groups (No/Yes).

Laboratory testing for MDR-PA

For *P. aeruginosa* identification, the clinical specimens from patients were cultured on blood agar and MacConkey agar at 33-35 °C and incubated for 16-18 hours. On blood agar, *P. aeruginosa* colonies show as beta-hemolytic or gamma-hemolytic and show as non-lactose fermented colonies on MacConkey agar. Standard biochemical tests were used for the identification of *P. aeruginosa*. The laboratory testing process was performed in the Department of Clinical Microbiology Laboratory, Roi Et Hospital.

Susceptibility tests for *MDR-PA* were used disc diffusion. Discs test consisted of amikacin (AK, 30 µg), ceftazidime (CAZ, 30µg), imipenem (IPM, 10µg), meropenem (MEM, 10 µg), doripenem (DOR, 10 µg), piperacilin/tazobactam (TZP, 110 µg), gentamicin (GN, 10 µg), co-trimoxazole (SXT), and ciprofloxacin (CIP, 5 µg). The quality controls for the antibiotic susceptibility tests were used *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

MDR-PA was defined as P. aeruginosa resistant to more than three groups of antibiotics consisting of aminoglycoside, carbapenem, cephalosporin, beta-lactam plus beta-lactamase inhibitor, and quinolone.

Statistical analysis

The analyses were used descriptive statistics and Pearson's Chi-square test for homogeneity testing between cases and controls. Bivariate and multivaritate analyses were used logistic regression to investigate the associations among the factors of MDR-PA infection. Bivariate analyses used simple logistic regression for each variable and outcome; *p*-value tested at less than or equal to 0.25 from Wald's test were entered into the initial model of multivariate analysis using a backward elimination method. A *p*-value from Wald's test of less than 0.05 was considered significant. The final model was adjusted by sex and age and presented using the adjusted odds ratio (OR_A), 95% confident interval, and *p*-value. Statistical significance was set at *p*-value < 0.05.

Results

General characteristic of cases and controls

Of the 110 cases, 51.82% were male and 48.18% were female. The mean age was 61.82 years (SD = 15.67), 91.82% had graduated from primary school, 76.36% had a spouse, 67.27% worked in agriculture, 40.91% had been admitted to the intensive care unit, and 54.55% had been admitted for longer than 7 days. Most of the 110 control subjects were male (56.36 %), the mean age was 55.0 years (SD = 16.09), 71.82% had graduated from primary school, 60.00% had a spouse, 57.27% worked in agriculture, 45.45% had been admitted to the intensive care unit, and 61.82% had been admitted for 7 days or less (Table 1).

Table 1 General characteristic of cases and controls

Variable	Cases (n = 110)	Controls (n = 110)	*p*-value
	n(%)	n(%)	
Sex			0.499
Male	57(51.82)	62(56.36)	
Female	53(48.18)	48(43.64)	
Age (years)			0.004
≤ 60	49(44.55)	70(63.64)	
> 60	61(55.45)	40(36.36)	
Mean ± SD	61.82 ± 15.67	55.01 ± 16.09	
Min, Max	18, 87	17, 86	
Education			<0.001
Primary school	101(91.82)	79(71.82)	
High school	6(5.45)	12(10.91)	
Bachelor' s degree	3(2.73)	19(17.27)	
Marital status			0.005
Single	20(18.18)	21(19.09)	
Spouse	84(76.36)	66(60.00)	
Divorced	2(1.82)	4(3.64)	
Widowed	4(3.64)	19(17.27)	

Table 1 General characteristic of cases and controls

Variable	Cases (n = 110)	Controls (n = 110)	*p*-value
	n (%)	n (%)	
Occupational			0.162
Agriculture	74(67.27)	63(57.27)	
Business	3(2.73)	2(1.82)	
Government officer	4(3.64)	11(10.00)	
Employee	13(11.82)	21(19.09)	
Unemployed	16(14.55)	13(11.82)	
Ward admitted to			0.004
Surgical	12(10.91)	14(12.73)	
Medicine	35(31.82)	32(29.09)	
Intensive care unit	45(40.91)	50(45.45)	
Others	18(16.36)	14(12.73)	
Duration of admittance	50(45.45)	68(61.82)	0.015
≤ 7 days	60(54.55)	42(38.18)	
> 7 days			

Note: *p*-value from chi-square test.

The antibiotic susceptibility pattern of MDR-PA

The 110 case of MDR-PA were susceptible to amikacin 80.4%, ceftazidime 18.3%, ciprofloxacin 19.9%, gentamicin 21.8%, imipenem 18.2%, meropenem 17.4%, doripenem 14.4%, and 100 % resistance to cotrimoxazole (Table 2).

Table 2 The antibiotic susceptibility pattern of MDR-PA

Antibiotics	% Sensitivity (n = 110)
Amikacin	80.4
Ciprofloxacin	19.9
Ceftazidime	18.3
Gentamicin	21.8
Imipenem	18.2
Meropenem	17.4
Doripenem	14.4
Piperacilin/Tazobactam	14.00
Cotrimoxazole	0.00

Univariate analysis risk factors for MDR-PA

The univariate analysis indicated that the risk factors for MDR-PA infection were patient-aged more than 60 years old (OR = 2.17, 95%CI = 1.26 - 3.74), patient admitted to the intensive care unit (OR = 2.77, 95%CI = 1.32 - 5.81), duration admitted longer than 7 days (OR_{Adj} = 1.94, 95%CI = 1.13 - 3.32), patient with complications (OR = 3.27, 95%CI = 1.83 - 5.86), patient had an endotracheal tube (OR_{Adj} = 2.44, 95%CI = 1.36 - 4.38), and a mechanical ventilator (OR_{Adj} = 3.04, 95% CI = 1.65 - 5.59) (Table 3).

Table 3 Univariate analysis factors associated with multidrug-resistant *P. aeruginosa* infection

Variable	Cases (n = 110)	Controls (n = 110)	OR_C (95%CI)	*p*-value
	n (%)	n (%)		
Sex				
Male	57 (51.82)	62(56.36)	1.0	
Female	53(48.18)	48(43.64)	1.20(0.70-2.74)	0.499
Age (years)				
≤ 60	49(44.55)	70(63.64)	1.0	
> 60	61(55.45)	40(36.36)	2.17(1.26-3.74)	0.005
Ward admitted to				
Surgical	12(10.91)	14(12.73)	1.0	
Medicine	35(31.82)	32(29.09)	0.83(0.48-1.42)	0.496
Intensive care unit	45(40.91)	50(45.45)	2.77(1.32-5.81)	0.007
Others	18(16.36)	14(12.73)	0.62(0.3 9-1.26)	0.191
Underlying diseases				
No	55(50.00)	63(57.27)	1.0	
Diabetes mellitus	26(23.64)	17(15.45)	0.57(0.28-1.16)	0.122
Hypertension	17(15.45)	13(11.82)	0.67(0.29-1.49)	0.327
Chronic kidney disease	8(7.27)	8(7.27)	0.87(0.30-2.48)	0.799
Cardiovascular disease	2(1.82)	6(5.45)	2.16(0.50-13.51)	0.250
Others	2(1.82)	3(2.73)	1.30(0.21-8.12)	0.772
Complication				
No	25(22.73)	54(49.09)	1.0	
Yes	85(77.27)	56(50.91)	3.27(1.83-5.86)	<0.001
Duration of admitted				
≤ 7 days	50(45.45)	68(61.82)	1.0	
> 7 days	60(54.55)	42(38.18)	1.94(1.13-3.32)	0.015
Surgery				
No	83(75.45)	86(78.18)	1.0	
Yes	27(24.55)	24(21.82)	1.65(0.62-2.18)	0.632
Urinary catheter				
No	71(64.55)	74(67.27)	1.0	
Yes	39(35.45)	36(32.73)	1.12(0.64-1.97)	0.670
Endotracheal tube				
No	64(58.18)	85(77.27)	1.0	
Yes	46(41.82)	25(22.73)	2.44(1.36-4.38)	0.003

Table 3 Univariate analysis factors associated with multidrug-resistant *P. aeruginosa* infection (cont.)

Variable	Cases (n = 110)	Controls (n = 110)	OR_C (95%CI)	*p*-value
	n (%)	n (%)		
Mechanical Ventilator				
No	64(58.18)	89(80.91)	1.0	
Yes	46(41.82)	21(19.09)	3.04(1.65-5.59)	<0.001
Prior antimicrobial receiving				
No	78(70.91)	81(73.64)	1.0	
Yes	32(29.09)	29(26.36)	1.14(0.63-2.06)	0.651

Multivariate analysis of risk factors for MDR-PA

The multivariate analysis indicated the risk factors for MDR-PA infection were: patient aged more than 60 years old (OR_{Adj} = 2.06, 95%CI = 1.14 - 3.71), duration admitted longer than 7 days (OR_{Adj} = 2.43, 95%CI = 1.28 - 4.60), patient had an endotracheal tube (OR_{Adj} = 2.61, 95%CI = 1.42 - 4.80), and a mechanical ventilator (OR_{Adj} = 3.14, 95%CI = 1.67 - 5.88) (Table 4).

Table 4 Multivariate analysis factors associated with multidrug-resistant *P. aeruginosa* infection

Variable	Cases (n = 110)	Controls (n = 110)	OR_C(95%CI)	OR_A(95%CI)	*p*-value
	n (%)	n (%)			
Age (years)					
≤ 60	49(44.55)	70(63.64)	1.0	1.0	0.016
> 60	61(55.45)	40(36.36)	2.17(1.26-3.74)	2.06(1.14-3.71)	
Complication					
No	25(22.73)	54(49.09)	1.0	1.0	0.112
Yes	85(77.27)	56(50.91)	3.27(1.83-5.86)	1.73(0.87-3.43)	
Duration of admittance					
≤ 7 days	50(45.45)	68(61.82)	1.0	1.0	0.006
> 7 days	60(54.55)	42(38.18)	1.94(1.13-3.32)	2.43(1.28-4.60)	
Endotracheal tube					
No	64(58.18)	85(77.27)	1.0	1.0	0.002
Yes	46(41.82)	25(22.73)	2.44(1.36-4.38)	2.61(1.42-4.80)	
Mechanical Ventilator					
No	64(58.18)	89(80.91)	1.0	1.0	<0.001
Yes	46(41.82)	21(19.09)	3.04(1.65-5.59)	3.14(1.67-5.88)	

Note: Adjusted by gender and age; OR_C, Crude odds ratio; OR_A, Adjusted odds ratio; 95% CI, 95% confidence interval; *p*-value from multiple logistic regression

Discussion

The prevalence of MDR-PA infection in Thailand is increasing[8]. However, it is rare to find reports on the risk factors of MDR-PA infection among Thai population. Our study identified that patients aged more than 60 years, who had been admitted to hospital for longer than 7 days and underwent procedures for an endotracheal tube and a mechanical ventilator were important factors for risk of infection. These were consistent with previous studies reporting that hospitalized patients were at high risk of MDR-PA infection[4,9-12]. A study in the United States of America reported that a lower age of patients reduced the risk of MDR-PA infection[11]. This was similar to the finding in the current study. The current study was also consistent with research in Spain that found that the underlying severity of the disease, multi-organ dysfunction syndrome, and severity of acute clinical illness resulted in those patients having a high risk of MDR-PA infection[13,14]. Specifically, the current study found that patients with complications were 1.73 times more at risk of MDR-PA infection. However, patients who had surgery had no risk of MDR-PA infection, which was contrasted by a study in France that found that patients who underwent surgical treatment were 1.9 times more at risk of MDR-PA infection[9]. The current study identified that patients who underwent a procedure with an endotracheal tube and a mechanical ventilator were at high risk of MDR-PA infection, which was consistent with studies reported in Israel, the United States of America, China, and France where a hospital stay and requirements for procedures, mechanical ventilation, and tracheal intubation insertion were important risk factors for MDR-PA infection[4,10,11,15].

Conclusion

Our study findings showed that patients aged more than 60 years and who had been admitted to hospital for more than 7 days and underwent procedures with an endotracheal tube and a mechanical ventilator were important risk factors for MDR-PA infection.

Take home messages

Patients in the high risk should have special care from medical team to prevent MDR-PA infection especially patient that underwent with medical procedures.

Conflicts of interest

The authors declare no conflict of interest.

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